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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,267	SCHNECK ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,10,12-19,23-41,46-49,51-65,71-87 and 143-145* is/are pending in the application.

4a) Of the above claim(s) *16-19,30-36,51-59 and 71-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,10,12-15,23-29,37-41,46-49,60-65 and 143-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 3/23/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 4-41 and 46-65), and species of solid support that is a bead, a T lymphocyte affecting molecule that is an antibody that specifically binds to CD28, an MHC class I complex comprising at least two fusion proteins, wherein a first fusion protein comprises a first MHC class I alpha chain and a first Ig heavy chain and wherein a second fusion protein comprises a second MHC class I alpha chain and a second Ig heavy chain, wherein the first and second Ig heavy chains associate to form the MHC lass I molecular complex, wherein the MHC class I molecular complex comprises a first MHC class I peptide binding cleft and a second MHC class I peptide binding cleft in Applicant's response filed 7/31/06.

Claims 1, 3, 7, 14, 23, 24, 46-49, 64 and newly added claims 143-145 read upon the elected species.

Upon consideration of the prior art cited in this Office Action below, the species recited in instant claims 10, 12, 13, 15, 25-29, 37-41, 60-62 and 65 are also being examined.

Claims 1, 3, 7, 10, 12-15, 23-29, 37-41, 46-49, 60-62, 64, 65 and 143-145 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1, 3, 7, 10, 12-15, 23-29, 37-41, 46-49, 60-62, 64, 65 and 143-145 is deemed to be the filing date of the instant application, *i.e.,* 7/14/03, as the parent application serial no. 60/395,781 does not support the claimed limitations of the instant application. Application serial no. 60/395,781 provides support for the limitations of a solid support that is a bead that has attached thereto, a co-stimulatory molecule that is an anti-CD28 antibody and an MHC class I molecule that consists of the extracellular regions of the MHC class I alpha chain as well as β2m, and wherein the MHC class I alpha chain extracellular regions are attached at the C-terminal end to Ig constant region comprising the hinge region, and wherein the MHC class I-Ig fusion proteins form dimers. Application serial no. 60/395,781 does not provide support for the limitation "rigid solid support" or for "an artificial particle" except for a bead, nor for the limitation wherein the fusion protein "comprises at least one MHC class I peptide binding cleft" or "comprises at least one antigen binding cleft" wherein the fusion protein does not consist of the β2m and wherein it is not part of a dimer, nor for the limitation wherein the fusion protein comprises an MHC class I alpha chain and an Ig heavy chain wherein the fusion protein comprises the entire MHC class I alpha chain and the entire Ig heavy chain, not just the extracellular regions or the Ig hinge and constant regions, respectively, and wherein the dimeric fusion proteins do not further comprise β2m, nor for the limitation "at least T cell affecting molecule" that is not a co-stimulatory molecule or anti-CD28, nor for the T cell

co-stimulatory molecules recited in instant claims 23 and 24, except for anti-CD28, nor for wherein "the at least one antigen presenting complex comprises an MHC class II peptide binding cleft" as well as the limitations pertaining to the MHC class II fusion proteins recited in the instant claims, nor the adhesion molecules or T cell growth factors recited in the instant claims. The said parent application does not provide support for the limitation "particle" except wherein the particle is a bead.

The following are new grounds of rejection necessitated by Applicant's amendment filed 3/23/07 and by Applicant's IDS filed 4/27/07.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,268,411 B1 (of record) in view of WO 97/28191 A1 (of record) and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03) and by an admission in the instant specification at [83].

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

U.S. Patent No. 6,268,411 B1 discloses MHC class I/Ig divalent chimeric complexes or MHC class II/Ig chimeric complexes comprising at least four fusion proteins, in the latter instance, wherein the MHC class II α chain is fused to the Ig heavy chain and the β chain is fused to the Ig light chain at the carboxy-terminus of the extracellular domains. U.S. Patent No. 6,268,411 B1 discloses that an identical antigenic peptide from a tumor associated antigen, a viral or infectious agent associated antigen, an autoimmune disease associated antigen, an alloantigen or xenogantigen, or an allergy associated antigen may be bound in the MHC molecule in the peptide binding groove. U.S. Patent No. 6,268,411 B1 discloses that the peptide/MHC/Ig complexes may be conjugated or fused to a toxin or a molecule such as a lymphokine or other effector molecule(s) that can stimulate an immune response and may be affixed to a solid substrate such as a glass or plastic slide or tissue culture plate or latex, PVC or polystyrene bead or a viral particle. U.S. Patent No. 6,268,411 B1 discloses that the viral particles that carry the complexes may also contain saline, a pharmaceutically acceptable carrier. U.S. Patent No. 6,268,411 B1 discloses that the MHC class I α chain is fused to the Ig heavy chain. U.S. Patent No. 6,268,411 B1 discloses that the peptide/MHC/ig complexes can be used to stimulate T cells, and that immobilization of the said complexes can stimulate antigen specific T cells. U.S. Patent No. 6,268,411 B1 discloses that thus, these reagents can be used to selectively activate antigen specific T cells either *in vitro* or *in vivo*. U.S. Patent No. 6,268,411 B1 discloses that the Ig heavy chain may comprise a variable region. U.S. Patent No. 6,268,411 B1 discloses that the chimeric protein may be conjugated to a toxin such as ricin or *Pseudomonas* toxin when T cell inactivation or killing is desired (especially abstract, Figure 1A, column 3 at lines 5-15, 30-64, column 8 at lines 9-27, column 9 at lines 24-67, column 10 at lines 12-67, column 11 at lines 1-62, column 16 at lines 55-67, claims).

U.S. Patent No. 6,268,411 B1 does not disclose wherein the at least one T cell affecting molecule is a T cell costimulatory molecule such as B7-1 or B7-2, or anti-CD28 antibody, wherein the at least one T cell affecting molecule is an adhesion molecule such as ICAM-1 or LFA-3, nor wherein the said molecule is IL-2, nor wherein the MHC class II β chain is fused to the Ig heavy chain and the MHC class II α chain is fused to the Ig light chain.

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains, and that the complexes may further comprise an antigenic peptide. WO/97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at

lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

Latouche *et al* teach that signaling through the CD28 receptor provides a powerful costimulatory signal following engagement of the B7-1 or B7-2 ligand, and that the adhesion molecule ICAM-1 provides a syngergistic signal, while LFA-3 can also mediate costimulatory as well as adhesion functions. Latouche *et al* further teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28. Latouche *et al* teach addition of IL-2 to artificial APC comprising the MHC, costimulatory and adhesion molecules when stimulating T cells (especially Introduction on page 405, paragraph spanning columns 1-2 on page 408, materials and methods section on page 409 at the first full paragraph of column 1).

The admission in the instant specification at [83] discloses that ricin and *Pseudomonas* toxins are apoptosis-inducing molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support and composition thereof disclosed by U.S. Patent No. 6,268,411 B1 to also include a costimulatory molecule such as that taught by WO 97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 molecules taught by WO/97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally ICAM-1 and/or LFA-3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both U.S. Patent No. 6,268,411 B1 and WO/97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO/97/28191 A1 and Latouche *et al* teach that signaling through the CD28 receptor either through interaction with B7-1 or B7-2 or anti-CD28 antibody provides a powerful co-stimulatory signal.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a T cell growth factor such as IL-2 taught by Latouche *et al* to the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate T cells *in vitro* because Latouche *et al* teach addition of IL-2 to the artificial APC comprising the MHC complexes, costimulatory molecules and adhesion molecules when stimulating T cells *in vitro*.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the MHC class II/Ig complexes as per the teaching of WO 97/28191 A1 with the α chain fused to the Ig light chain and the β chain fused to the Ig heavy chain or as disclosed by U.S. Patent No. 6,268,411 B1 with the light and heavy chains fused to β and α MHC class II chains, respectively.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO/97/28191 A1 teaches and U.S. Patent No. 6,268,411 B1 discloses that the MHC class II/Ig complexes may be constructed in either of these ways.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a toxin on the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 6,268,411 B1 teaches that pseudomonas or ricin toxin(s) may be used in conjunction with MHC-Ig fusion proteins when antigen-specific T cell inactivation or killing is desired. It is noted by the Examiner that the instant specification at [83] discloses that ricin and *Pseudomonas* toxins are apoptosis-inducing molecules.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in applicant's amendment filed 3/23/07 on pages 21-27.

It is the Examiner's position that: (1) the references are being argued separately, (2) that U.S. Patent No. 6,268,411 B1 discloses using an MHC construct along with a lymphokine or other effector molecule(s) that can stimulate an immune response and may be affixed to a solid substrate such as a glass or plastic slide or tissue culture plate or latex, PVC or polystyrene bead or a viral particle, and Latouche *et al* teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28, the same molecules that are engaged by MHC and B7-1 or B7-2, respectively, (3) Latouche *et al* teach that the factors important for T cell stimulation in their system are MHC level and density and maintenance of the expression of the MHC/peptide complexes, lack of competing irrelevant MHC/peptide complexes, factors which are preserved when using solid-support bound MHC/peptide complexes, (4) Albani is not of record in the instant rejection, and while Albani may teach a system for stimulation of T cells, so does the instant combination of references, (5) Qi *et al* is not of record in the IDS filed 7/14/03, (6) a prima facie case of obviousness has been established and one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated herein.

6. Claims 1, 3, 7, 10, 12-15, 23-29, 37-41, 46-49, 60-62, 64, 65 and 143-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,015,884 (IDS reference in the form 1449 filed 7/14/03) in view of in view of WO 97/35991 A1 (of record), WO 97/28191 A1 (of record) and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

U.S. Patent No. 6,015,884 discloses MHC class II/Ig/peptide heterodimers bound with high avidity to T cells bearing their cognate receptors. U.S. Patent No. 6,015,884 discloses divalent complexes comprising the said heterodimers wherein the said complexes are comprised of at least 4 chimeric proteins, *i.e.,* the MHC class II β chain extracellular regions fused to IgG heavy chain comprising the intact variable region and the MHC class II α chain extracellular regions fused to IgG light chain, and wherein the class II MHC binding sites contain an identical antigenic peptide, such as from a viral antigen, tumor antigen, alloantigen, or autoimmune antigen, and wherein the complexes may be immobilized on a substrate to stimulate antigen specific T cell responses, said substrate being a solid substrate such as a plate or bead. U.S. Patent No. 6,015,884 further discloses that the chimeric proteins may be linked or fused to a toxin or solid matrix, and may be comprised in a pharmaceutical composition with saline and optionally with cytokines such as IL-2, αIFN and IFNγ. U.S. Patent No. 6,015,884 discloses that MHC class II chimeric proteins and complexes may be constructed using heavy and light chains of Ig. U.S. Patent No. 6,015,884 discloses that the MHC-Ig constructs may be used in conjunction with toxins such as ricin or Pseudomonas extotoxin when antigen-specific T cell killing or inactivation is desired, or with other apoptosis inducing agents such as Fas ligand, or with cytokines such as IL-15, IL-10, or IFN-α when T cell activation is desired (especially abstract, Figure 1, summary of the invention, first 30 paragraphs of detailed description of the invention, column 27 at lines 56-61, claims).

U.S. Patent No. 6,015,884 does not disclose wherein the solid support further comprises at least one T cell affecting molecule that is a co-stimulatory molecule or an adhesion molecule recited in the instant claims, nor wherein the solid support comprises an MHC class I/Ig/peptide divalent complex rather than an MHC class II/Ig/peptide complex.

WO 97/35991 A1 teaches divalent MHC class I or II molecules that are comprised of MHC class I or MHC class II extracellular regions linked or fused to Ig heavy and light chains, and further that the MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses. WO 97/35991 A1 teaches that the MHC class II divalent molecules comprise two fusion proteins that comprise an Ig heavy chain and an extracellular domain of an MHC class II β chain, and two fusion proteins that comprise and Ig light chain and an extracellular domain of an MHC class II α chain. WO 97/35991 A1 teaches that the Ig heavy or light chain may comprise a variable region sequence (especially abstract, page 8 at lines 3-28, paragraph spanning pages 9-10, page 15 at lines 21-22, page 20 at lines 3-12, page 23 at lines 13-27, Figure 1).

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains or to IgG heavy and light chains, and that the complexes may further comprise an antigenic peptide. WO 97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

Latouche *et al* teach that signaling through the CD28 receptor provides a powerful costimulatory signal following engagement of the B7-1 or B7-2 ligand, and that the adhesion molecule ICAM-1 provides a syngergistic signal, while LFA-3 can also mediate costimulatory as well as adhesion functions. Latouche *et al* further teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28. Latouche *et al* teach addition of IL-2 to artificial APC comprising the MHC, costimulatory and adhesion molecules when stimulating T cells (especially Introduction on page 405, paragraph spanning columns 1-2 on page 408, materials and methods section on page 409 at the first full paragraph of column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support disclosed by U.S. Patent No. 6,015,884 to have also included a costimulatory molecule such as that taught by WO 97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 molecules taught by WO/97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally the adhesion molecule(s) ICAM-1 and/or LFA-3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both U.S. Patent No. 6,015,884 and WO 97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO 97/28191 A1 and Latouche *et al* teach that signaling through the CD28 receptor either through interaction with B7-1 or B7-2 or anti-CD28 antibody provides a powerful co-stimulatory signal and WO 97/35991 A1 teaches immobilizing the MHC/Ig complexes on a solid support.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a T cell growth factor such as IL-2 taught by Latouche *et al* or as disclosed by U.S. Patent No. 6,015,884 to the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate T cells *in vitro* because Latouche *et al* teach and U.S. Patent No. 6,015,884 discloses addition of IL-2 to compositions comprising the MHC complexes when stimulating T cells *in vitro*.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support disclosed by U.S. Patent No. 6,015,884 to have substituted the class I/Ig complexes taught by the WO references for the class II/Ig complexes, and to have added a T cell growth factor such as IL-2 taught by Latouche *et al* or as disclosed by U.S. Patent No. 6,015,884 to the solid support or to have modified the solid support disclosed by U.S. Patent No. 6,015,884 to have also included a costimulatory molecule such as that taught by WO 97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 molecules taught by WO/97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally the adhesion molecule(s) ICAM-1 and/or LFA-3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate $CD8^+$ T cells *in vitro* for the reasons enunciated herein for stimulation using the MHC class II/Ig complexes.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a toxin on the solid support, or to have included a cytokine such as IL-15, IL-10 or TNF-α on the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 6,268,411 B1 teaches that pseudomonas or ricin toxin(s) may be used in conjunction with MHC-Ig fusion proteins when antigen-specific T cell inactivation or killing is desired and that a cytokine such as IL-15, IL-10 or TNF-α may be used in conjunction with the MHC-Ig fusion proteins when T cell stimulation is desired.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in applicant's amendment filed 3/23/07 on pages 21-27.

It is the Examiner's position that: (1) the references are being argued separately, (2) that U.S. Patent No. 6,015,884 discloses the complexes may be immobilized on a substrate to stimulate antigen specific T cell responses, said substrate being a solid substrate such as a plate or bead, WO 97/35991 A1 teaches MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses, and Latouche *et al* teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28, the same molecular complexes that are engaged by MHC and B7-1 or B7-2, respectively, (3) Latouche *et al* teach that the factors important for T cell stimulation in their system are MHC level and density and maintenance of the expression of the MHC/peptide complexes, lack of competing irrelevant MHC/peptide complexes, factors which are preserved when using solid-support bound MHC/peptide complexes, (4) Albani is not of record in the instant rejection, and while Albani may teach a system for stimulation of T cells, so does the instant combination of references, (5) Qi *et al* is not of record in the IDS filed 7/14/03, (6) a prima facie case of obviousness has been established and one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated herein.

7. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 41, 46-49, 60-62, 64, 65 and 143-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/35991 A1 (of record) in view of WO 97/28191 A1 (of record) and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03).

WO 97/35991 A1 teaches divalent MHC class I or II molecules that are comprised of MHC class I or MHC class II extracellular regions linked or fused to Ig heavy and light chains, and further that the MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses. WO 97/35991 A1 teaches that the MHC class II divalent molecules comprise two fusion proteins that comprise an Ig heavy chain and an extracellular domain of an MHC class II β chain, and two fusion proteins that comprise and Ig light chain and an extracellular domain of an MHC class II α chain. WO 97/35991 A1 teaches that the Ig heavy or light chain may comprise a variable region sequence (especially abstract, page 8 at lines 3-28, paragraph spanning pages 9-10, page 15 at lines 21-22, page 20 at lines 3-12, page 23 at lines 13-27, Figure 1).

WO 97/35991 A1 does not teach wherein the divalent MHC class I molecules are attached to a solid support and wherein the solid support further comprises at least one lymphocyte affecting molecule that is a co-stimulatory molecule.

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO 97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains or to Ig heavy and light chains, and that the complexes may further comprise an antigenic peptide. WO 97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches linkage of an antigenic peptide to the divalent class II MHC molecules, said antigenic peptide derived from moth cytochrome C amino acid residues 81-101 for stimulating T cells, and that T cells respond to peptide antigen in the context of either class I or class II MHC molecules, said peptide antigens being from viral or tumor or transplantation antigens, said peptide antigens binding in the antigen binding site of MHC molecules. WO 97/28191 A1 teaches formulation of the said complexes in a pharmaceutically acceptable carrier such as saline (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

Latouche *et al* teach that signaling through the CD28 receptor provides a powerful costimulatory signal following engagement of the B7-1 or B7-2 ligand, and that the adhesion molecule ICAM-1 provides a syngergistic signal, while LFA-3 can also mediate costimulatory as well as adhesion functions. Latouche *et al* further teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28. Latouche *et al* teach addition of IL-2 to compositions comprising the MHC complexes when stimulating T cells *in vitro*. (especially Introduction on page 405, paragraph spanning columns 1-2 on page 408, materials and methods on page 409, column 1, first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have immunobilized the MHC class I/Ig fusion dimers taught by WO 97/35991 A1 and by WO 97/28191 A1 on a solid support as taught for the MHC class II/Ig fusion dimers taught by WO 97/35991 A1, and to have also immobilized a costimulatory molecule such as taught by WO 97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 molecules taught by WO 97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally ICAM-1 and/or LFA-3, and further to have loaded the MHC/Ig fusion dimers with antigenic peptide as taught by WO 97/28191 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both WO 97/35991 A1 and by WO 97/28191 A1 teach MHC class I/Ig dimers for stimulating CD8+ T cells, WO 97/35991 A1 teaches that MHC/Ig dimers may be immobilized on a solid substrate such as a bead for stimulating T cells, both WO 97/28191 A1 and Latouche *et al* teach that signaling through the CD28 receptor either through interaction with B7-1 or B7-2 or anti-CD28 antibody provides a powerful co-stimulatory signal.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the beads comprising the fusion dimers and other molecules in saline such as taught by WO 97/28191 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to store the beads in a compatible buffered solution because saline or PBS is taught by WO 97/28191 A1 to be compatible with the protein component and is a commonly available carrier as was known to one of ordinary skill in the art at the time the invention was made.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a T cell growth factor such as IL-2 taught by Latouche *et al* to the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate T cells *in vitro* because Latouche *et al* teach addition of IL-2 to compositions comprising the MHC complexes when stimulating T cells *in vitro*.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in applicant's amendment filed 3/23/07 on pages 21-27.

It is the Examiner's position that: (1) the references are being argued separately, (2) WO 97/35991 A1 teaches MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses, and Latouche *et al* teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28, the same molecular complexes that are engaged by MHC and B7-1 or B7-2, respectively, (3) Latouche *et al* teach that the factors important for T cell stimulation in their system are MHC level and density and maintenance of the expression of the MHC/peptide complexes, lack of competing irrelevant MHC/peptide complexes, factors which are preserved when using solid-support bound MHC/peptide complexes, (4) Albani is not of record in the instant rejection, and while Albani may teach a system for stimulation of T cells, so does the instant combination of references, (5) Qi *et al* is not of record in the IDS filed 7/14/03, (6) a prima facie case of obviousness has been established and one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated herein.

8. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,268,411 B1 (of record) in view of WO 99/42597 A1 (IDS referenced filed 4/27/07) and WO 97/28191 A1 (of record) and by an admission in the instant specification at [83].

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing

that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

U.S. Patent No. 6,268,411 B1 discloses MHC class I/Ig divalent chimeric complexes or MHC class II/Ig chimeric complexes comprising at least four fusion proteins, in the latter instance, wherein the MHC class II α chain is fused to the Ig heavy chain and the β chain is fused to the Ig light chain at the carboxy-terminus of the extracellular domains. U.S. Patent No. 6,268,411 B1 discloses that an identical antigenic peptide from a tumor associated antigen, a viral or infectious agent associated antigen, an autoimmune disease associated antigen, an alloantigen or xenogantigen, or an allergy associated antigen may be bound in the MHC molecule in the peptide binding groove. U.S. Patent No. 6,268,411 B1 discloses that the peptide/MHC/Ig complexes may be conjugated or fused to a toxin or a molecule such as a lymphokine or other effector molecule(s) that can stimulate an immune response and may be affixed to a solid substrate such as a glass or plastic slide or tissue culture plate or latex, PVC or polystyrene bead or a viral particle. U.S. Patent No. 6,268,411 B1 discloses that the viral particles that carry the complexes may also contain saline, a pharmaceutically acceptable carrier. U.S. Patent No. 6,268,411 B1 discloses that the MHC class I α chain is fused to the Ig heavy chain. U.S. Patent No. 6,268,411 B1 discloses that the peptide/MHC/ig complexes can be used to stimulate T cells, and that immobilization of the said complexes can stimulate antigen specific T cells. U.S. Patent No. 6,268,411 B1 discloses that thus, these reagents can be used to selectively activate antigen specific T cells either *in vitro* or *in vivo*. U.S. Patent No. 6,268,411 B1 discloses that the Ig heavy chain may comprise a variable region. U.S. Patent No. 6,268,411 B1 discloses that the chimeric protein may be conjugated to a toxin such as ricin or *Pseudomonas* toxin when T cell inactivation or killing is desired (especially abstract, Figure 1A, column 3 at lines 5-15, 30-64, column 8 at lines 9-27, column 9 at lines 24-67, column 10 at lines 12-67, column 11 at lines 1-62, column 16 at lines 55-67, claims).

U.S. Patent No. 6,268,411 B1 does not disclose wherein the at least one T cell affecting molecule is a T cell costimulatory molecule such as B7-1 or B7-2, or anti-CD28 antibody, wherein the at least one T cell affecting molecule is an adhesion molecule such as ICAM-1 or LFA-3, nor wherein the said molecule is IL-2, nor wherein the MHC class II β chain is fused to the Ig heavy chain and the MHC class II α chain is fused to the Ig light chain.

WO 99/42597 A1 teaches human MHC class I (*i.e.*, HLA) constructs comprising class I heavy chain (*i.e.*, α chain), β2m and antigenic peptide and further comprising a carrier molecule, the said carrier molecule being a spherical or porous bead such as for example, polystyrene, silica, PGA, PLA, PSA, PLGA, PLSA or PGSA, and the construct further comprising biologically active molecules such as CD40, I-CAM adhesion proteins, or the CD28 binding co-stimulatory molecules B7-1 or B7-2 or the adhesion molecule LFA-3. WO 99/42597 A1 teaches pharmaceutical compositions comprising the said constructs and further comprising a pharmaceutically acceptable excipient.

WO 99/42597 A1 teaches that multivalent constructs of the invention have far greater avidity for the cognate TCR, and far greater biological activity than monovalent MHC binding domains, or even divalent or tetravalent MHC binding domain constructs. WO 99/42597 A1 teaches that the constructs are useful for isolating T cells of a particular specificity, for adoptive immunotherapy to stimulate T cells *ex vivo*, to activate T cell *in vivo* (especially abstract, page 4 at the first paragraph, paragraph spanning pages 7-8, page 8 at lines 3-30, page 9 at lines 1-31, page 10 at lines 1-30, page 11, page 16 at lines 17-21 and 27-31, page 17 at lines 1-16, page 18 at lines 8-18, page 19 at lines 1-6 and 13-30, page 20 at lines 1-24, page 25 at lines 6-17 and 30-31, page 26 at lines 1-9, page 35 at lines 15-31, page 36 at lines 1-15, page 39 at lines 8-31, page 40 at lines 1-30, pages 41-43 and page 44 at lines 1-8, page 45 at lines 6-30, pages 46-50, page 48 at lines 9-24, page 51 at lines 1-13).

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains, and that the complexes may further comprise an antigenic peptide. WO/97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

The admission in the instant specification at [83] discloses that ricin and *Pseudomonas* toxins are apoptosis-inducing molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support and composition thereof disclosed by U.S. Patent No. 6,268,411 B1 as per the teaching of WO 99/42597 A1 to comprise biologically active molecules such as CD40, I-CAM adhesion proteins, or the CD28 binding co-stimulatory molecules B7-1 or B7-2 or the adhesion molecule LFA-3 and the bead materials and also as taught by WO 97/28191 A1 that costimulatory molecules B7-1 or B7-2 are necessary to induce clonal expansion of T cells specific for MHC/peptide complexes.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both U.S. Patent No. 6,268,411 B1 and WO/97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO/97/28191 A1 and both WO/97/28191 and WO 99/42597 A1 teach costimulatory molecules B7-1 and B7-2 are used in concert with MHC molecules to stimulate T cells, and WO 99/42597 A1 teaches that multivalent constructs of the invention have far greater avidity for the cognate TCR, and far greater biological activity than monovalent MHC binding domains, or even divalent or tetravalent MHC binding domain constructs. WO 99/42597 A1 teaches that the constructs are useful for isolating T cells of a particular specificity, for adoptive immunotherapy to stimulate T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the MHC class II/Ig complexes as per the teaching of WO 97/28191 A1 with the α chain fused to the Ig light chain and the β chain fused to the Ig heavy chain or as disclosed by U.S. Patent No. 6,268,411 B1 with the light and heavy chains fused to β and α MHC class II chains, respectively.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO/97/28191 A1 teaches and U.S. Patent No. 6,268,411 B1 discloses that the MHC class II/Ig complexes may be constructed in either of these ways.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a toxin on the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 6,268,411 B1 teaches that pseudomonas or ricin toxin(s) may be used in conjunction with MHC-Ig fusion proteins when antigen-specific T cell inactivation or killing is desired. It is noted by the Examiner that the instant specification at [83] discloses that ricin and *Pseudomonas* toxins are apoptosis-inducing molecules.

9. Claims 1, 3, 7, 10, 12-15, 23-29, 37-41, 46-49, 60-62, 64, 65 and 143-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,015,884 B1 (of record) in view of WO 99/42597 A1 (IDS referenced filed 4/27/07) and WO 97/28191 A1 (of record).

U.S. Patent No. 6,015,884 discloses MHC class II/Ig/peptide heterodimers bound with high avidity to T cells bearing their cognate receptors. U.S. Patent No. 6,015,884 discloses divalent complexes comprising the said heterodimers wherein the said complexes are comprised of at least 4 chimeric proteins, *i.e.,* the MHC class II β chain extracellular regions fused to IgG heavy chain comprising the intact variable region and the MHC class II α chain extracellular regions fused to IgG light chain, and wherein the class II MHC binding sites contain an identical antigenic peptide, such as from a viral antigen, tumor antigen, alloantigen, or autoimmune antigen, and wherein the complexes may be immobilized on a substrate to stimulate antigen specific T cell responses, said substrate being a solid substrate such as a plate or bead. U.S. Patent No. 6,015,884 further discloses that the chimeric proteins may be linked or fused to a toxin or solid matrix, and may be comprised in a pharmaceutical composition with saline and optionally with cytokines such as IL-2, αIFN and IFNγ. U.S. Patent No. 6,015,884 discloses that MHC class II chimeric proteins and complexes may be constructed using heavy and light chains of Ig. U.S. Patent No. 6,015,884 discloses that the MHC-Ig constructs may be used in conjunction with toxins such as ricin or Pseudomonas extotoxin when antigen-specific T cell killing or inactivation is desired, or with other apoptosis inducing agents such as Fas ligand, or with cytokines such as IL-15, IL-10, or IFN-α when T cell activation is desired (especially abstract, Figure 1, summary of the invention, first 30 paragraphs of detailed description of the invention, column 27 at lines 56-61, claims).

U.S. Patent No. 6,015,884 does not disclose wherein the solid support further comprises at least one T cell affecting molecule that is a co-stimulatory molecule or an adhesion molecule recited in the instant claims, nor wherein the solid support comprises an MHC class I/Ig/peptide divalent complex rather than an MHC class II/Ig/peptide complex.

WO 99/42597 A1 teaches human MHC class I (*i.e.*, HLA) constructs comprising class I heavy chain (*i.e.*, α chain), β2m and antigenic peptide and further comprising a carrier molecule, the said carrier molecule being a spherical or porous bead such as for example, polystyrene, silica, PGA, PLA, PSA, PLGA, PLSA or PGSA, and the construct further comprising biologically active molecules such as CD40, I-CAM adhesion proteins, or the CD28 binding co-stimulatory molecules B7-1 or B7-2 or the adhesion molecule LFA-3. WO 99/42597 A1 teaches pharmaceutical compositions comprising the said constructs and further comprising a pharmaceutically acceptable excipient. WO 99/42597 A1 teaches that multivalent constructs of the invention have far greater avidity for the cognate TCR, and far greater biological activity than monovalent MHC binding domains, or even divalent or tetravalent MHC binding domain constructs.

WO 99/42597 A1 teaches that the constructs are useful for isolating T cells of a particular specificity, for adoptive immunotherapy to stimulate T cells *ex vivo*, to activate T cell *in vivo* (especially abstract, page 4 at the first paragraph, paragraph spanning pages 7-8, page 8 at lines 3-30, page 9 at lines 1-31, page 10 at lines 1-30, page 11, page 16 at lines 17-21 and 27-31, page 17 at lines 1-16, page 18 at lines 8-18, page 19 at lines 1-6 and 13-30, page 20 at lines 1-24, page 25 at lines 6-17 and 30-31, page 26 at lines 1-9, page 35 at lines 15-31, page 36 at lines 1-15, page 39 at lines 8-31, page 40 at lines 1-30, pages 41-43 and page 44 at lines 1-8, page 45 at lines 6-30, pages 46-50, page 48 at lines 9-24, page 51 at lines 1-13).

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains or to Ig heavy and light chains, and that the complexes may further comprise an antigenic peptide. WO/97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support and composition thereof disclosed by U.S. Patent No. 6,015,884 as per the teaching of WO 99/42597 A1 to comprise biologically active molecules such as CD40, I-CAM adhesion proteins, or the CD28 binding co-stimulatory molecules B7-1 or B7-2 or the adhesion molecule LFA-3 and the bead materials and also as taught by WO 97/28191 A1 that costimulatory molecules B7-1 or B7-2 are necessary to induce clonal expansion of T cells specific for MHC/peptide complexes.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both U.S. Patent No. 6,015,884 and WO/97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO/97/28191 A1 and both WO/97/28191 and WO 99/42597 A1 teach costimulatory molecules B7-1 and B7-2 are used in concert with MHC molecules to stimulate T cells, and WO 99/42597 A1 teaches that multivalent constructs of the invention have far greater avidity for the cognate TCR, and far greater biological activity than monovalent MHC binding domains, or even divalent or tetravalent MHC binding domain constructs.

WO 99/42597 A1 teaches that the constructs are useful for isolating T cells of a particular specificity, for adoptive immunotherapy to stimulate T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the MHC class II/Ig complexes as per the teaching of WO 97/28191 A1 with the α chain fused to the Ig light chain and the β chain fused to the Ig heavy chain or as disclosed by U.S. Patent No. 6,015,884 with the light and heavy chains fused to β and α MHC class II chains, respectively.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO/97/28191 A1 teaches and U.S. Patent No. 6,015,884 discloses that the MHC class II/Ig complexes may be constructed in either of these ways.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a toxin on the solid support, or to have included a cytokine such as IL-15, IL-10 or TNF-α on the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 6,268,411 B1 teaches that pseudomonas or ricin toxin(s) may be used in conjunction with MHC-Ig fusion proteins when antigen-specific T cell inactivation or killing is desired and that a cytokine such as IL-15, IL-10 or TNF-α may be used in conjunction with the MHC-Ig fusion proteins when T cell stimulation is desired.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-104 of U.S. Patent No. 6,268,411 B1 (IDS reference in the Form 1449 filed 7/14/03) in view of in view of WO 97/35991 A1, WO 97/28191 A1 and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03).

Instant claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are drawn to a solid support comprising a least one lymphocyte affecting molecule and at least one molecular complex that when bound to an antigen engages a unique clonotypic receptor, wherein the said complex comprises at least two MHC class I or at least four MHC class II/Ig fusion proteins.

Claims 1-104 of U.S. Patent No. 6,268,411 B1 are drawn to a composition comprising at least two chimeric proteins, wherein each chimeric protein comprises an MHC molecule and an Ig chain.

Claims 1-104 of U.S. Patent No. 6,268,411 B1 do not recite wherein the said composition is linked to a solid support.

The complexes recited in claims 1-104 of U.S. Patent No. 6,268,411 B1 are encompassed by the complexes of the solid support recited in the instant claims.

WO 97/35991 A1 teaches divalent MHC class I or II molecules that are comprised of MHC class I or MHC class II extracellular regions linked or fused to Ig heavy and light chains, and further that the MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses. WO 97/35991 A1 teaches that the MHC class II divalent molecules comprise two fusion proteins that comprise an Ig heavy chain and an extracellular domain of an MHC class II β chain, and two fusion proteins that comprise and Ig light chain and an extracellular domain of an MHC class II α chain. WO 97/35991 A1 teaches teaches that the Ig heavy or light chain may comprise a variable region sequence (especially abstract, page 8 at lines 3-28, paragraph spanning pages 9-10, page 15 at lines 21-22, page 20 at lines 3-12, page 23 at lines 13-27, Figure 1).

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains, and that the complexes may further comprise an antigenic peptide. WO 97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

Latouche *et al* teach that signaling through the CD28 receptor provides a powerful costimulatory signal following engagement of the B7-1 or B7-2 ligand, and that the adhesion molecule ICAM-1 provides a syngergistic signal, while LFA-3 can also mediate costimulatory as well as adhesion functions. Latouche *et al* further teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28. Latouche *et al* teach addition of IL-2 to artificial APC comprising the MHC, costimulatory and adhesion molecules when stimulating T cells (especially Introduction on page 405, paragraph spanning columns 1-2 on page 408, materials and methods section on page 409 at the first full paragraph of column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the complexes and composition thereof recited in the claims of U.S. Patent No. 6,268,411 B1 to immobilize the said complexes on a solid support as taught by WO 97/35991 A1 for the MHC/Ig divalent complexes and to have also included a costimulatory molecule such as that taught by WO/97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 molecules taught by WO/97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally ICAM-1 and/or LFA-3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because both the claims of U.S. Patent No. 6,268,411 B1 recite and WO 97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO 97/28191 A1 and Latouche *et al* teach that signaling through the CD28 receptor either through interaction with B7-1 or B7-2 or anti-CD28 antibody provides a powerful co-stimulatory signal, and WO 97/35991 A1 teaches immobilizing the MHC/Ig complexes on a solid support.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a T cell growth factor such as IL-2 taught by Latouche *et al* to the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate T cells *in vitro* because Latouche *et al* teach addition of IL-2 to the artificial APC comprising the MHC complexes, costimulatory molecules and adhesion molecules when stimulating T cells *in vitro*.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 3/23/07 on page 27, briefly that an obviousness-type double patenting analysis parallels an analysis under 35 USC 103(a) except that the disclosure of the cited patent is not considered prior art, and thus arguments made to rebut the rejection under 35 USC 103(a0 apply with equal force to the obviousness-type double patenting rejections and are incorporated herein.

It is the Examiner's position that the instant rejection stands, and the Examiner's comments to Applicant's arguments to the 103(a) rejections of record enunciated supra in this Office Action apply herein.

12. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are directed to an invention not patentably distinct from claims 1-104 of commonly assigned U.S. Patent No. 6,268,411 B1 in view of in view of WO 97/35991 A1, WO/97/28191 A1 and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03) as enunciated above at item #16 of this Office Action.

13. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,268,411 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

14. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 4-10 of U.S. Patent No. 6,015,884 in view of in view of WO 97/35991 A1, WO 97/28191 A1 and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03).

Instant claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are drawn to a solid support comprising a least one lymphocyte affecting molecule and at least one molecular complex that when bound to an antigen engages a unique clonotypic receptor, wherein the said complex comprises at least two MHC class I or at least four MHC class II/Ig fusion proteins.

Claims 1, 2 and 4-10 of U.S. Patent No. 6,015,884 are drawn to a molecular complex which comprises at least four fusion proteins, including wherein each chimeric protein comprises an MHC class II molecule α or β chain fused to an Ig chain.

Claims 1, 2 and 4-10 of U.S. Patent No. 6,015,884 do not recite wherein the said complex is linked to a solid support, nor wherein the solid support further comprises at least one lymphocyte affecting molecule as recited in the instant claims.

WO 97/35991 A1 teaches divalent MHC class I or II molecules that are comprised of MHC class I or MHC class II extracellular regions linked or fused to Ig heavy and light chains, and further that the MHC class II divalent molecules may be immobilized on a solid substrate such as beads or tissue culture plates to stimulate antigen specific T cell responses. WO 97/35991 A1 teaches that the MHC class II divalent molecules comprise two fusion proteins that comprise an Ig heavy chain and an extracellular domain of an MHC class II β chain, and two fusion proteins that comprise and Ig light chain and an extracellular domain of an MHC class II α chain. WO 97/35991 A1 teaches that the Ig heavy or light chain may comprise a variable region sequence (especially abstract, page 8 at lines 3-28, paragraph spanning pages 9-10, page 15 at lines 21-22, page 20 at lines 3-12, page 23 at lines 13-27, Figure 1).

WO 97/28191 A1 teaches that peptide/MHC complexes on the surface of antigen presenting cells (APC) will only induce clonal expansion of a T cell line specific for the MHC bound peptide if the APC also deliver co-stimulatory signals. WO/97/28191 A1 teaches complexes of MHC class I or MHC class II molecules can be used to induce T cells, the complexes comprising the extracellular regions of the MHC molecule linked or fused to an immunoglobulin heavy and light constant region domains, and that the complexes may further comprise an antigenic peptide. WO 97/28191 A1 teaches that if DNA encoding the complexes is transfected into a cell, a co-stimulatory molecule should also be co-transfected, and that co-stimulatory molecules are B7[-1] or B7-2. WO 97/28191 A1 teaches that the α chain can be fused to the Ig light chain and the β chain can be fused to the Ig heavy chain (especially page 2 at lines 16-19, page 3 at lines 7-30, page 9 at lines 5-14, page 13 at lines 5-9, page 18 at lines 14-30, page 25 at

lines 11-26, paragraph spanning pages 33-34, page 34 at lines 9-19 and lines 27-31, page 38 at lines 1-9, Figures 1B and 1C).

Latouche *et al* teach that signaling through the CD28 receptor provides a powerful costimulatory signal following engagement of the B7-1 or B7-2 ligand, and that the adhesion molecule ICAM-1 provides a syngergistic signal, while LFA-3 can also mediate costimulatory as well as adhesion functions. Latouche *et al* further teach that T cells may be expanded by incubation with beads coated with anti-CD3 and anti-CD28 antibodies to engage the TCR and CD28. Latouche *et al* teach addition of IL-2 to artificial APC comprising the MHC, costimulatory and adhesion molecules when stimulating T cells (especially Introduction on page 405, paragraph spanning columns 1-2 on page 408, materials and methods section on page 409 at the first full paragraph of column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the complexes recited in the claims of U.S. Patent No. 6,015,884 to immobilize the said complexes on a solid support as taught by WO 97/35991 A1 for the MHC/Ig divalent complexes and to have also included a costimulatory molecule such as that taught by WO 97/28191 A1 to be necessary to induce clonal expansion of T cells specific for MHC/peptide complexes such as the B7-1 or B7-2 moleculés taught by WO/97/28191 A1 or the anti-CD28 antibody taught by Latouche *et al*, and optionally ICAM-1 and/or LFA-3.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a solid substrate comprising an MHC complex that would be effective in stimulating CD8+ T cells because the claims of U.S. Patent No. 6,015,884 recite and WO 97/28191 A1 teach MHC class /Ig dimers for stimulating T cells, and both WO 97/28191 A1 and Latouche *et al* teach that signaling through the CD28 receptor either through interaction with B7-1 or B7-2 or anti-CD28 antibody provides a powerful co-stimulatory signal, and WO 97/35991 A1 teaches immobilizing the MHC/Ig complexes on a solid support.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a T cell growth factor such as IL-2 taught by Latouche *et al* to the solid support.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate T cells *in vitro* because Latouche *et al* teach addition of IL-2 to the artificial APC comprising the MHC complexes, costimulatory molecules and adhesion molecules when stimulating T cells *in vitro*.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 3/23/07 on page 27, briefly that an obviousness-type double patenting analysis parallels an analysis under 35 USC 103(a) except that the disclosure of the cited patent is not considered prior art, and thus arguments made to rebut the rejection under 35 USC 103(a0 apply with equal force to the obviousness-type double patenting rejections and are incorporated herein.

It is the Examiner's position that the instant rejection stands, and the Examiner's comments to Applicant's arguments to the 103(a) rejections of record enunciated supra in this Office Action apply herein.

15. Claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, 65 and 143-145 are directed to an invention not patentably distinct from claims 1, 2 and 4-10 of commonly assigned U.S. Patent No. 6,015,884 in view of in view of WO 97/35991 A1, WO/97/28191 A1 and Latouche *et al* (Nature Biotechnology. 18: 405-409, 2000, IDS reference in the Form 1449 filed 7/14/03) as enunciated above at item #19 of this Office Action.

16. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,015,884, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

17. No claim is allowed.

18. The following is in regard to Applicant's Form 1449 filed 4/27/07.

a. As per the Waiver of the Copy Requirement in 37 CFR 1.98 for Cited Pending U.S. Patent Applications (1287 Off. Gaz. Pat. Office 163, October 19, 2004), a copy of each cited pending U.S. patent application, or portion of the application which caused it to be listed is no longer required to be filed with an IDS if the cited application is stored in the IFW system and the cited information is limited to the specification, including the claims and drawings of the cited pending U.S. application. Accordingly, the reference application serial no. 09/642,660 cited in Applicant's Form 1449 filed 4/27/07 has been considered only as to the extent of the specification, including the claims, and drawings, and the specification.

Applicant is reminded that if the cited information from the pending application is an Office Action, affidavit, or IDS filed in the cited pending U.S. application which is not part of the specification, a copy of the cited paper is required.

b. The reference EP0352701 has not been considered by the Examiner because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of said patent listed that is not in the English language.

c. The other references crossed out in said IDS have not been considered because they were not provided by Applicant.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

In addition, Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 4/27/07 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 24, 2007

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